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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,460	LUNSFORD ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22,24-36 and 51-80* is/are pending in the application.

4a) Of the above claim(s) *17,22,24,25 and 27-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,18-21,26,33-36 and 51-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *18 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

GB

DETAILED ACTION

This office action is in response to an amendment and request for continued examination filed 9/22/05. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/22/05 has been entered.

The instant claims were last amended in an amendment filed 8/4/03. At this time, claims 23 and 37-50 were cancelled. Claims 1, 8, 34, 35 and 51 were amended. Claims 17, 22, 24, 25 and 27-32 were withdrawn. Claims 52-80 were added. Therefore, claims 1-22, 24-36 and 51-80 were pending in the application.

Rejoinder

In the office action mailed 8/12/04, claims 52-80 were withdrawn from consideration as being drawn to a non-elected claimed invention. However, upon reconsideration, claims 52-80 have been rejoined with claims 1-16, 18-21, 26, 33-36 and 51. Therefore, claims 1-16, 18-21, 26, 33-36 and 51-80 are under examination in this application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. Specifically, the rejections under 35 USC 102 and the judicially created doctrine of

obviousness-type double patenting were overcome by applicants' arguments in the amendment filed 9/22/05.

Priority

Support for the limitation that a microparticle comprises in addition to a polymeric matrix and a nucleic acid, a lipid is not found in the priority documents 09/003,253 filed 1/6/1998, 60/035,983, filed 1/22/1997 or PCT/US98/01499 filed 1/22/1998. These applications are drawn to microparticles comprising polymeric matrices and nucleic acids. While these applications consider use of lipids as stabilizers present in excipients or formulations, the applications do not contemplate a microparticle comprising a lipid. This limitation has been added to prior applications 09/321,346, filed 5/27/1999 and 09/266,463, filed 3/11/1999. Therefore, a priority date of 3/11/1999 will be attributed to the instant claims.

As well, in the reference to the prior application inserted, as the first sentence of the specification of this application, all provisional and nonprovisional parent application(s) (whether patented or abandoned) should be listed. In the instant case, the information has been provided in a transmittal letter filed 7/18/01. To be complete, the reference should be inserted as the first line of the specification. Furthermore, this reference in the instant application should be updated. For example, if a parent application (i.e. 09/321,346) has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 5, line 18. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. **This is a new objection.**

Claim Objections

Claim 8 is objected to because of the following informalities: Claim 8, line 15-16 recites a polypeptide consisting of at least two peptides "sharing an overlapping sequence". Rejection under 35 USC 112, second paragraph for use of the term "at least" following "consisting of" is below. However, the claims are also objected to for recitation that the at least two peptides are "sharing" an overlapping sequence. The specification teaches that at least two peptides of (b) are arranged in a series wherein the sequence of the carboxy terminus of one peptide overlaps with the sequence at the N-terminus of the next amino acid. So in fact the peptides are not "sharing" overlapping sequences but are linked because they are generated from overlapping sequences. Appropriate clarification is required. **This is a new objection.**

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 18-21, 26, 33-36 and 51-80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment. This is a New Matter rejection.**

The limitation that "the microparticle does not comprise a liposome" has been added to claims 1, 8, 52 and 72. Applicant has not indicated where support for this limitation is found. The examiner has been unable to find literal support in the originally filed specification for the term "the microparticle does not comprise a liposome". Rather the specification only teaches that the lipid components of the microparticle "preferably are not present in liposomes that encapsulate (i.e. surround) the microparticles". This teaches that the microparticle is not encapsulated by liposomes, the scope of which is not commensurate with the recitation that the microparticle does not comprise a liposome. Therefore, the limitation of adding "the microparticle does not comprise a liposome" is impermissible NEW MATTER.

Claims 60 and 61 added in the amendment filed 8/4/03 are drawn to a preparation comprising a plurality of microparticles wherein the microparticles further comprise a carbohydrate. The disclosure teaches that the microparticles are in an excipient or formulation comprising a carbohydrate. However, the recitation that the microparticle comprises a carbohydrate suggests a relationship between the microparticle and the carbohydrate, which is not so disclosed in the specification. That the specification teaches that the microparticle can be formulated in a carbohydrate based solution means that the microparticle can be comprised

within a carbohydrate but does not teach that the microparticle comprise a carbohydrate. Therefore, the limitation of adding "the preparation of claim 52 further comprising a second lipid" is impermissible NEW MATTER.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 8-16, 18-21, 26, 33-36, 58 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Claims 8 and 15 are vague and indefinite in that the metes and bounds of "a polypeptide consisting of at least two peptides are unclear. Use of the term "at least" following "consisting of" is inappropriate as "consisting of" is closed language while "at least" is open. Therefore it is unclear if the polypeptide can be more than made up of more than two peptides or not.

Claim 58 is vague and indefinite in that the metes and bounds of "further comprising a second lipid" are unclear. It is unclear if the lipid must be in complex with the microparticle such that each microparticle of the preparation comprises a second lipid or if the preparation comprises the second lipid as a stabilizer or excipient. The disclosure teaches that the microparticles themselves comprise a second lipid (claim 13) but also that the microparticles can be contained in a buffer or excipient that comprises a lipid. Therefore, it is unclear if in claim 58 the second lipid is limited to in complex with the microparticles or not.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 6, 7, 52-55, 65, 66, 70 and 75 are rejected under 35 U.S.C. 102(a) as being anticipated by Lambert et al (Biochimie, 1998, Vol 80, pages 969-976; see entire document).

Lambert et al teach a microparticle less than 20 microns in diameter (see e.g. page 972, col 2, paragraph 2) comprising a polymeric matrix, a lipid and a nucleic acid (see e.g. page 970, col 1, paragraph 4- col 2, paragraph 3) and preparations of these microparticles (see e.g. table 1) as recited in claims 1, 7 and 52. Given the broadest interpretation that can be afforded " a stabilizer" and absent evidence to the contrary, the complex formation between the lipids and the nucleic acid functions to protect the nucleic acid as recited in claim 6 and thus is a "stabilizer". Lambert et al teach antisense oligonucleotides associated with nanoparticles and the cationic lipid cetyltrimethylammonium (CTAB), (see e.g. page 970, col 2, paragraph 3) as recited in claims 53-55. The particles are resuspended in medium (see table 1), which is a pharmaceutically acceptable carrier as recited in claim 70. The nucleic acid is an oligonucleotide as recited in claim 75. The polymeric matrix is polyisobutylcyanoacrylate (see

e.g. bridging paragraph col 1-2, page 970), which is a synthetic biodegradable copolymer as evidenced by Balland et al (see e.g. page 131, paragraph 1) as recited in claims 65 and 66.

Claims 1, 6, 7, 52-55, 65, 66, 70 and 75 are rejected under 35 U.S.C. 102(b) as being anticipated by Balland et al (NATO ASI Series, 1996, Vol 290, pages 131-142; see entire document).

Balland et al teach a microparticle less than 20 microns in diameter (see e.g. page 132, paragraph 4) comprising a polymeric matrix, a lipid and a nucleic acid (see e.g. page 132, paragraph 4- 5) and preparations of these microparticles (see e.g. page 133, paragraph 4) as recited in claims 1, 7 and 52. Given the broadest interpretation that can be afforded " a stabilizer" and absent evidence to the contrary, the complex formation between the lipids and the nucleic acid functions to protect the nucleic acid as recited in claim 6 and thus is a "stabilizer" (see e.g. page 131, paragraph 1). The lipid is cetyltrimethylammonium (CTAB) and is cationic (see e.g. page 131, paragraph 2) as recited in claims 53-55. The particles are resuspended in PBS (see page 133, paragraph 4), which can be a pharmaceutically acceptable carrier as recited in claim 70. The nucleic acid is an oligonucleotide as recited in claim 75. The polymeric matrix is polyisohexylcyanoacrylate (PIHCA), which is a synthetic biodegradable copolymer (see e.g. page 131, paragraph 1 and page 132, paragraph 4) as recited in claims 65 and 66. Balland et al teach that the nucleic acid was protected against enzymatic degradation (see table 1) and uptake by cells was dramatically increased (figure 2) by complex formation with CTAB.

Claims 1-9, 11, 13, 16, 18, 21, 26, 33, 34, 51-54, 56, 58, 59, 62, 64, 65, 70-76 are rejected under 35 U.S.C. 102(e) as being anticipated by Paphadjopolous et al (US 6,210,707; see entire document).

Papahadjopolous et al teach a lipidic microparticle comprising lipids and nucleic acids (see e.g. abstract) and polymeric matrices (see e.g. col 3, line 50-67). The invention is designed to provide lipid:nucleic acid complexes that have increased shelf life, for transfection of mammalian cells *in vitro* or *in vivo* or *ex vivo* (see e.g. col 18, line 50-53). The lipidic-microparticles can be made with amphiphilic cationic lipids complexed with nucleic acids and polymer (see e.g. col 7, line 16-29). The microparticles can be part of a preparation and are each less than 11 microns (see e.g. col 8,line 34-41 and col 18, line 29-47) as recited in claims 1, 7, 52 and 64. The nucleic acid can be part of an expression cassette that is disclosed as being expression vectors or plasmids, which are circular, expressing polypeptides (see e.g. col 8, line 21-26, col 11, line 41-51) as recited in claim 2-4, 62 and 71. The lipids of the microparticle can be amphiphilic cationic lipids such as phospholipids (see e.g. col 6, line 41-51) and the microparticles and hence the preparations of microparticles are also associated with a second lipid or neutral helper lipid (see e.g. col 3, line 31-50) as recited in claim 9, 11, 13, 53, 54, 56 and 58. The expression cassettes encode polypeptides such as β-globin, which comprise at least 7 amino acids identical to at least a fragment of a naturally occurring mammalian protein as recited in claim 8 and 16. The microparticles further comprise a targeting moiety (see e.g. abstract) as recited in claim 5 and a stabilizer (hydrophilic polymer attached to a hydrophobic side chain, see abstract) as recited in claim 6 and 59. The targeting moiety can be attached to the microparticle during production or can be expressed by the nucleic acid of the microparticle. The targeting

moieties are immunogenic peptides as recited in claims 18 and 21 such as ligands, growth factors or cytokines (see e.g. col 7, line 4-16, col 15, line 31-52) and Paphadjopolous specifically describes targeting moieties that recognize MHC complexes (i.e. MHC I) (see e.g. col 15, line 23-col 16, line 11), peptides that bind MHC molecules as recited in claim 8 (b). The instant specification describes proteinaceous antigenic determinants as containing an epitope, which limitation is met by the use of ligands on the microparticle. Thus a microparticle with such a targeting moiety and a nucleic acid encoding an antigenic polypeptide such as hGH (see e.g. col 19, line 32-37) meets the claim limitations as recited in claim 72 and 73. Paphadjopolous further contemplate administration of the microparticles to mammals for gene therapy in which the microparticle is administered in an effective amount at a target sites such as the circulatory system (see e.g. col 4, line 51-66 and col 8, line 8, line 64-67) as recited in claim 51. Specifically, Paphadjopolous describe targeting the microparticles to immune cells (see e.g. col 22, line 46-64), which would result in elicitation of an immune response as recited in claim 34.

Furthermore, it is contemplated that the microparticle encode a trafficking signal (see e.g. col 12, line 4-12) as recited in claim 26 or an oligonucleotide (see e.g. col 19, line 10-31) as recited in claim 74, 75 and 76. The microparticle can be a preparation of particles and is in a pharmaceutically acceptable carrier (see e.g. col 8,line 34-41) as recited in claim 33 and 70 . The polymer can be spermine, a biodegradable polymer (see e.g. col 3, line 50-52) as recited in claim 65.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8, 12, 52, 57, 58, 72 and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Debs et al (US 5,827,703; see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The lipid is phosphatidylcholine or phosphatidylethanolamine.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous teaches that the lipids are phospholipids but does not teach that these phospholipids are specifically phosphatidylcholine or phosphatidylethanolamine.

Debs et al teach methods for introducing genes into cells by complexing DNA to lipid carriers (see e.g. abstract). The lipidic carriers are preferably phosphatidylcholine and phosphatidylethanolamine as these are suitable compounds for repeated injection into mammalian hosts.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use phosphatidylcholine or phosphatidylethanolamine as taught by Debs et al in the lipid microparticles taught by Paphadjopolous et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles using phospholipids to generate lipid:nucleic acid complexes and because Debs et al teach that it is within the ordinary

skill of the art to use phosphatidylcholine and phosphatidylethanolamine to form lipid:nucleic acid complexes for gene delivery. One would have been motivated to do so in order to receive the expected benefit of forming particles with phosphatidylcholine or phosphatidylethanolamine that are suitable for repeated administration in mammals. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 8, 10, 52 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Balland et al (NATO ASI Series, 1996, Vol 290, pages 131-142; see entire document) in view of Paphadjopolous et al (US 6,210,707; see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The lipid is CTAB and the nucleic acid comprises at least 7 amino acids identical to at least a fragment of a naturally occurring mammalian protein.

The teachings of Balland et al and Paphadjopolous et al are described above and are applied as before except;

Neither teach a microparticle comprising CTAB and a nucleic acid comprising at least 7 amino acids identical to at least a fragment of a naturally occurring mammalian protein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to complex the expression cassettes taught by Paphadjopolous et al with CTAB as taught by Balland et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles comprising nucleic acid expressing polypeptides for delivery to mammals and because Balland et al teach that it is within the ordinary skill of the art

to adsorb nucleic acids to CTAB and polymeric matrices for gene delivery. One would have been motivated to do so in order to receive the expected benefit of microparticles designed to express therapeutic proteins such as viral inhibitors, blood proteins, enzymes or to replace deficient genes (see Paphadjopolous col 19, line 10-31) that are protected against enzymatic degradation and whose uptake by cells is dramatically increased by complex formation with CTAB (see Balland et al table 1 and figure 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 8, 14, 15, 19, 20 and 34-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Fikes et al (US 6,534,482; see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The microparticles are designed to deliver arrayed peptides.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the microparticles are designed to deliver arrayed peptides.

Fikes et al teach development of nucleic acid vaccines comprising multiple MHC I and II epitopes employing a peptide or arrays of peptides for use as an immunogenic composition (see e.g. abstract). One or more MHC I epitopes (CTL epitopes) are fused together (see e.g. col 5, line 18-31). The peptides are synthesized with overlapping sequences that are then shared to form a multiepitope compound in which the peptides are then arranged in tandem (see e.g. col

21, line 17-30). The epitopes are contained on an expression vector (see e.g. col 20, line 32-45) and introduced into mammals to elicit immune responses following delivery to the mucosal tissue such as vaginal tissue (see e.g. bridging paragraph col 23-24). The DNA is delivered for therapeutic purposes (see e.g. col 24, line 30-37).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the lipid microparticles taught by Paphadjopolous et al to deliver the nucleic acid encoding immunogenic peptides such as those that bind to MHC I molecules as taught by Fikes et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles, comprising nucleic acid encoding therapeutic compositions, for delivery to mammals and because Fikes et al teach that it is within the ordinary skill of the art to employ arrays of peptides in a plasmid expression vector for therapeutic purposes such as to elicit an immune response. One would have been motivated to do so in order to receive the expected benefit of using microparticles designed to provide lipid:nucleic acid complexes that have increased shelf life, for transfection of mammalian cells *in vitro* or *in vivo* or *ex vivo* (see Paphadjopolous et al, col 18, line 50-53) to deliver the immunogenic compositions that are effective in eliciting immune responses (see Fikes et al, col 24, line 30-37). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 52 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Hedley et al (US

5,783,567; see entire document) or Ando et al (J Pharmaceutical Sciences, 1999, pages 126-130;see entire document).

Applicants claim a microparticle comprising lipids and nucleic acids and polymeric matrices. The microparticles comprises nucleic acids of which at least 50% are supercoiled.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the microparticles comprises nucleic acids of which at least 50% are supercoiled.

Hedley et al teach a preparation of microparticles made up of a polymeric matrix and nucleic acids of which at least 50% are supercoiled (see e.g. abstract). The nucleic acid is supercoiled for more efficient transfection. Means are taught to protected the integrity of the nucleic acid such as minimizing shearing forces and limiting sonication (see e.g. col 8, line 2-12)

Ando et al teach use of supercoiled DNA that is 85% supercoiled as supercoiling of the DNA is essential for its bioactivity (see e.g. page 126, col 2, paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that at least 50% of the nucleic acid molecules in the microparticles taught by Paphadjopolous et al are supercoiled as taught by Hedley et al and Ando et al because Paphadjopolous et al teach that it is within the ordinary skill of the art to generate lipid microparticles for gene delivery complexed to microparticles and because Hedley et al and Ando et al teach that it is within the ordinary skill of the art to preserve the integrity of nucleic acid supercoiling. One would have been motivated to do so in order to receive the expected benefit of microparticles designed to improve transfection efficiency and bioactivity. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent

evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 52 and 66-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Paphadjopolous et al (US 6,210,707; see entire document) in view of Cleek et al (J Biomedical Materials Res, 1997, pages 525-530; see entire document) as evidenced by Manoharan et al (2005/0153337; see entire document).

Applicants claim a preparation comprising a plurality of microparticle each of which comprises lipids, nucleic acids and polymeric matrices. The polymeric matrix is PLGA wherein the ratio of lactic acid to glycolic acid is in a range of 1:2 to about 4:1 or about 65:35 by weight.

The teachings of Paphadjopolous are described above and are applied as before except;

Paphadjopolous does not teach that the polymeric matrix is PLGA wherein the ratio of lactic acid to glycolic acid is in a range of 1:2 to about 4:1 or about 65:35 by weight.

Cleek et al teach use of microparticles for inhibition of smooth muscle cell growth. The microparticles are comprised of nucleic acid and PLGA, one of the few synthetic biodegradable polymers approved for human clinical use (see e.g. page 525, col 2, paragraph 2). PLGA degradation *in vivo* occurs by random non-enzymatic hydrolysis of the polyester bonds along the polymeric backbone at a rate dependent on the copolymer ratio. As they are hydrolyzed to lactic acid and glycolic acid, they are processed normally by the metabolic pathway and eliminated as carbon dioxide (see e.g. page 525, col 2, paragraph 2). The biodegradable PLGA particles were formed in a 1:1 ratio which is in the range of 1:2 to 4:1 and is about 65:35 ratio given that the term "about" is a relative term for which the specification provides no definition. The PLGA

served as effective delivery agents (see e.g. page 529, col 2, paragraph 4). While Cleek et al do not teach that the ratio of lactic acid to glycolic acid is "by weight", classically synthesis of PLGA from lactic acid and glycolic acid involves a combination of the monomers "by weight' as evidenced by Manoharan et al (see e.g. paragraph 0873).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PLGA particles as taught by Cleek et al in the lipid microparticles taught by Paphadjopolous et al because Cleek et al teach that it is within the ordinary skill in the art to use PLGA to deliver nucleic acids to cells and because Paphadjopolous et al teach that it is within the ordinary skill of the art to complex synthetic polymers, i.e. PLGA, to nucleic acid for stable delivery to cells. One would have been motivated to do so in order to receive the expected benefit that the microparticles comprised of PLGA are among the few synthetic biodegradable polymers approved for human clinical use because they are hydrolyzed to lactic acid and glycolic acid, they are processed normally by the metabolic pathway and eliminated as carbon dioxide and they serve as effective delivery agents (see Cleek et al, page 525, col 2, paragraph 2 and page 529, col 2, paragraph 4). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

October 29, 2005